(b) a substance which is capable of specifically binding to the IPGs and inhibiting the release of histamine caused by the IPGs; or

C2

(c) a substance which is capable of competing with IPGs released from mast cells, basophils or eosinophils but which does not cause allergic stimulation of these cell types,

wherein the IPG antagonist acts specifically on mast cells, basophils or eosinophils.

C3

19. (Amended) The method of claim 18, comprising administering an effective amount of an IPG antagonist in a pharmaceutically acceptable excipient.

In accordance with the requirements of 37 C.F.R. § 1.121, a marked up version showing the changes to the claims, is attached herewith as Appendix A. For the Examiner's convenience, a complete claim set of the currently pending claims is also submitted herewith as Appendix B.

These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

REMARKS

The Status of the Claims.

Claims 1-9 and 15-20 are pending with entry of this amendment, claims 10-14 and 21-23 being cancelled. Claims 1 and 19 are amended herein. These amendments introduce no new matter and support is replete throughout the specification.

With respect to claim 1, support for "wherein the IPG antagonist acts specifically on mast cells, basophils or eosinophils" can be found throughout the specification. For example, *see*, specification at page 5, line 11 to page 6, line 19. Claim 19 has been amended to correct a typographical error.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The Election/Restriction Requirement.

Pursuant to a restriction requirement made final, Applicants cancel claims 10-14 and 21-23 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Claims 8 and 9 are withdrawn from consideration as drawn to a nonelected species. Upon the allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141.

The Drawings.

Applicants note that the drawings filed on August 9, 2000 have been accepted by the Examiner.

The Information Disclosure Statement.

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement (Form 1449) submitted on December 20, 2000. Applicants submit herewith a supplemental information disclosure statement, which incorporates references found on page 31 and 32 of the specification.

Objection to the Specification

The specification was objected to for not having an abstract on a separate sheet of paper. Applicants have amended the specification to include an abstract on a separate sheet of paper. Support for the abstract added on new page 35 of the application can be found on the front page of the corresponding WO 99/49855. Accordingly, the objection should be withdrawn.

Objection to the Claims

Claim 19 was objected to for misspelling the word "comprising." Applicants have amended claim 19 to correctly spell comprising. Accordingly, the rejection should be withdrawn.

35 U.S.C. §112, First Paragraph.

Claims 16-20 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled because "it would require undue experimentation for one of skill to predict which, if

any, IPG antagonist would be effective in a method of inhibiting release of an IPG from a mast cell, a basophil or an eosinophil, comprising exposing said cell to an IPG antagonist without more guidance from the specification." Action at page 4. Applicants traverse.

To be an enabling disclosure under § 112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. As the Examiner is no doubt aware, it is well-settled that:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the inventions must not be undue experimentation. "[T]he key word is 'undue,' not 'experimentation.'"

In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citations omitted).

Whether undue experimentation is required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry: (1) nature of the invention; (2) breadth of the claims; (3) predictability of the art; (4) state of the prior art; (5) presence of working examples; (6) amount of guidance presented; (7) relative skill of those in the art; and (8) quantity of experimentation necessary. *See id.*

Nature of the invention and the Breadth of the Claims

As pointed out by the Examiner, the invention relates to methods for inhibiting release of an IPG from a mast cell, a basophil or an eosinophil. Action at page 3. Specifically, claim 16 (upon which claims 17-20 depend) recites "a method for inhibiting release of an IPG from a mast cell, a basophil or an eosinophil, the method comprising exposing the mast cell, the basophil or the eosinophil to an IPG antagonist."

Unpredictability of the Art and State of the Prior Art

The Action alleges that "the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Without such guidance, the IPG antagonists effective in the claimed methods for inhibiting release of an IPG from a mast cell comprising exposing said cell to an IPG antagonist is unpredictable and experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue" based on the teaching of the disclosure. Action at page 4. Applicants traverse.

The invention relates to methods for inhibiting release of an IPG from a mast cell, a basophil or an eosinophil by exposing a mast cell, a basophil, or an eosinophil with an IPG antagonist. The enzyme GPI-PLD is involved in the release of IPG from the mast cell, basophil or

eosinophil surface following allergen stimulation. *See*, specification at page 6, lines 10-19, at page 11, lines 13-21 and at page 27, lines 17-30. The GPI-PLD enzyme cleaves IPGs for their release. *See*, specification at page 6, lines 10-19 and at page 11, lines 13-21. As stated in the specification, an inhibitor of GPI-PLD is one IPG antagonist. *Id.* GPI-PLD can be inactivated by, e.g., alkaline treatment. *See*, specification at page 28, line 1 to page 29, line 20. In addition, the reference cited by the Examiner, the '147 patent, discusses that "GPI-PLD activities were completely inactivated by antisera [directed to GPI-PLD]...." *See*, '147 patent at column 11, lines 4-12. The '147 patent was filed on March 31, 1992 and issued on May 23, 1995. The specification also cites a reference (Davitz et al., 1989), which describes an enzymatic assay for determining GPI-PLD activity. *See*, specification, at page 25, lines 7-9. Thus, inhibitors of GPI-PLD are not an unpredictable area of the art and were described in the art along with methods for determining GPI-PLD activity.

Furthermore, the specification provides guidance and examples (*see*, section below) for determining whether an IPG antagonist, e.g., an inhibitor of GPI-PLD, inhibits the release of IPG from a mast cell, basophil or eosinophil.

Working Examples and Guidance in the Specification

It is alleged in the Office Action, that "it would require undue experimentation for one of skill to predict which, if any, IPG antagonist would be effective in a method for inhibiting release of an IPG from a mast cell, a basophil, or an eosinophil, comprising exposing said cell to an IPG antagonist without more guidance from the specification." Action at page 4. The Examiner fails to take into consideration the extensive teachings in the specification relating to IPG activity, IPG antagonists, etc.

The specification provides that cells that are exposed to an IPG antagonist can inhibit release of IPGs from mast cells, basophils or eosinophils, e.g., in response to an allergen. *See*, specification at page 5, lines 18-22 and at page 10, line 25 to page 11, line 21. Examples of IPG antagonists given in the specification are antibodies capable of specifically binding to IPGs, specific inhibitors of the enzyme GPI-PLD (e.g., an anti GPL-PLD antibody), IPGs derived from other tissue (e.g., that do not cause histamine release), etc. *See*, specification at page 5, line 30 to page 7, line 7 and at page 10, line 25 to page 13, line 10. In relation to these antagonists, the specification provides pages of guidance of how to produce antibodies, e.g., at page 13, line 12 to page 15, line 29 and how to determine inhibitors of GPI-PLD. For example, inhibitors of the enzyme GPI-PLD can be determined by using assays that measure GPI-PLD activity. *See*, specification at page 25, lines 7-9.

The specification also provides guidance to determine whether a compound is an IPG antagonist. This determination can be done by measuring release of IPGs from a mast cell, a basophil or an eosinophil. *See*, specification at page 4, line 30 to page 5, line 3. For example, IPG release or inhibition of release can be measured using immunodetection, e.g., with antibodies against IPG (which are also described in the specification). *See*, specification at page 18, lines 4-13. Furthermore, IPGs can act as second messages for a variety of mediators and cytokines, e.g., histamine. *See*, specification at page 7, lines 9-23. Thus, one of skill can also measure release of IPGs and inhibition of release of IPGs from a cell by measuring mediator release from a mast cell, a basophil or an eosinophil. For example, IPG release or inhibition of release can be measured by using, e.g., a histamine assay as described in the specification, e.g., *see*, specification at page 19, line 28 to page 20, line 14. Alternatively, hexosaminidase release or inhibition of hexosaminidase release, which is a surrogate marker for histamine release, can also be used to measure IPG release or inhibition of release. *See*, specification at page 27, lines 4-8, and page 26, lines 6-9.

Accordingly, the specification provides guidance and working example to enable a person of skill in the art to practice the invention.

Level of Skill in the Art

Applicant reminds the Examiner that the level of skill in the art is high (typically a Ph.D. or higher). Determining which IPG antagonists that would be effective in a method for inhibiting release of an IPG from a mast cell, a basophil, or an eosinophil is a routine technical exercise for practitioners skilled in the art.

Amount of Experimentation

The determination of which IPG antagonists would be effective in a method for inhibiting release of an IPG from a mast cell, a basophil or an eosinophil comprising exposing a cell to an IPG antagonist, is a routine technical matter accomplished without undue experimentation by a practitioner skilled in the art. By following guidance in the specification, it is a mere technical exercise to determine which IPG antagonists would be effective in this method.

Conclusion

In light of the enabling disclosure not discussed or recognized in the Office Action, Applicant respectfully submits that the full scope of the invention as recited in claims 16-20 is enabled by the specification according to the requirements of 35 U.S.C. §112, and the rejection should be withdrawn.

35 U.S.C. §102.

Claims 1-7 and 15 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Huang et al. May 1995, (U.S. Patent No. 5,418,147) ("patent '147"). Patent '147 allegedly teaches "a method for making a composition comprising providing an effective amount of an IPG antagonist, specifically the elected species of an inhibitor of GPI-PLD comprising a monoclonal antibody generated against GPI-PLD, in a pharmaceutically acceptable excipient." Action at page 3. As the rejection applies to the amended claims, Applicants traverse.

With respect to claims 1-7 and 15, in order for a reference to anticipate an invention, anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." Kalman v. Kimberly-Clark Corp., 218 USPQ 781, 789 (Fed. Cir. 1983). Amended claim 1 recites "wherein the IPG antagonist acts specifically on mast cells, basophils or eosinophils." This element is also included in dependent claims 2-7 and 15 as well. These limitations are not found in patent '147. Patent '147 is directed to various aspects of glycosyl-phosphatidylinositol specific phospholipase D protein, e.g., it discloses nucleic acid sequences encoding a GPI-PLD protein and vectors including the nucleic acid sequences, the GPI-PLD protein, and antiserum and antibodies directed to GPL-PLD protein. *See*, patent '147 at abstract, column 11, lines 1-40, etc. Patent '147 does not disclose an IPG antagonist that acts specifically on mast cells, basophils or eosinophil, which are elements of claim 1. As a result, all the elements of amended independent claim 1 (and dependent claims 2-7 and 15) are not found in patent '147. Accordingly, the rejection of claims 1-7 and 15 with respect to 35 U.S.C. § 102(b) should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P.O. BOX 458
Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877

Respectfully submitted,

Paul B. Littlepage
Reg. No: 48,581

APPENDIX A

"MARKED UP" CLAIMS ILLUSTRATING THE AMENDMENTS MADE TO THE CLAIMS OF 09/601,971 WITH ENTRY OF THIS AMENDMENT

1. (Amended) A method for making a composition for the treatment of a condition mediated by the release of inositolphosphoglycans (IPGs) from mast cells, basophils or eosinophils, the method comprising providing an effective amount of an IPG antagonist in a pharmaceutically acceptable excipient, wherein the antagonist is:

(a) a substance which is capable of inhibiting release of the IPGs by inhibiting the enzyme GPI-PLD;

(b) a substance which is capable of specifically binding to the IPGs and inhibiting the release of histamine caused by the IPGs; or

(c) a substance which is capable of competing with IPGs released from mast cells, basophils or eosinophils but which does not cause allergic stimulation of these cell types,

wherein the IPG antagonist acts specifically on mast cells, basophils or eosinophils.

10. (Cancel) ~~An inositolphosphoglycan (IPG), which IPG is obtainable from mast cells, basophils or eosinophils, and which is capable of causing histamine release from mast cells, basophils or eosinophils.~~

11. (Cancel) ~~A method of screening for antagonists of an IPG, the method comprising:~~

~~(a) exposing at least one cell to a putative antagonist of an IPG, which IPG is capable of causing histamine release from mast cells, basophils or eosinophils; and~~

~~(b) evaluating a response to an IPG or release of an IPG by the at least one cell.~~

12. (Cancel) ~~The method of claim 11, comprising exposing at least one RBL-2H3 cell to a putative antagonist and evaluating a response to or release of an IPG by the at least one RBL-2H3 cell.~~

13. (Cancel) ~~The method of claim 11, comprising evaluating the response to or release of an IPG by a histamine release assay, a hexosaminidase assay, an N-acetyl-glucosaminidase assay or an IL-4 assay.~~

14. (Cancel) ~~An antagonist of an IPG obtained by the method of claim 11.~~

19. (Amended) The method of claim 18, ~~comoprising~~ comprising administering an effective amount of an IPG antagonist in a pharmaceutically acceptable excipient.

21. (Cancel) ~~A method for treating a condition mediated by the release of IPGs from mast cells, basophils or eosinophils, the method comprising treating a subject with an effective amount of an IPG antagonist.~~

22. (Cancel) ~~The method of claim 21, wherein the IPG antagonist comprises an anti-IPG antibody; a substance capable of inhibiting or preventing IPG release in mast cells, basophils or eosinophils; an inhibitor of the enzyme GPI-PLD; an antibody capable of inhibiting IPG release by inhibiting cleavage of the IPGs caused by the enzyme GPI-PLD; or a competitive antagonist of the IPGs released from mast cells, basophils or eosinophils.~~

23. (Cancel) ~~The method of claim 21, wherein the condition mediated by release of IPGs is atopic dermatitis, food hypersensitivity, allergy, early phase asthma, late phase asthma, allergic interstitial pneumonitis, eczema, environmental lung disease, or a disorder mediated by infiltration of mast cells, basophils or eosinophils or a cell within the mast cell, basophil or eosinophil lineages.~~

APPENDIX B

CLAIMS PENDING IN USSN 09/601,971 WITH ENTRY OF THIS AMENDMENT

1. (Amended) A method for making a composition for the treatment of a condition mediated by the release of inositolphosphoglycans (IPGs) from mast cells, basophils or eosinophils, the method comprising providing an effective amount of an IPG antagonist in a pharmaceutically acceptable excipient, wherein the antagonist is:

(a) a substance which is capable of inhibiting release of the IPGs by inhibiting the enzyme GPI-PLD;

(b) a substance which is capable of specifically binding to the IPGs and inhibiting the release of histamine caused by the IPGs; or

(c) a substance which is capable of competing with IPGs released from mast cells, basophils or eosinophils but which does not cause allergic stimulation of these cell types,

wherein the IPG antagonist acts specifically on mast cells, basophils or eosinophils.

2. The method of claim 1, wherein the condition mediated by release of IPGs is atopic dermatitis, food hypersensitivity, allergy, early phase asthma, late phase asthma, allergic interstitial pneumonitis, eczema, environmental lung disease, or a disorder mediated by infiltration of mast cells, basophils or eosinophils or a cell within the mast cell, basophil or eosinophil lineages.

3. The method of claim 1 or 2, wherein the IPG antagonist is an anti-IPG antibody.

4. The method of claim 1 or 2, wherein the IPG antagonist is a substance capable of inhibiting or preventing IPG release in mast cells, basophils or eosinophils in response to an allergen.

5. The method of claim 4, wherein the antagonist is an inhibitor of the enzyme GPI-PLD.

6. The method of claim 5, wherein the antagonist is an antibody capable of inhibiting IPG release by inhibiting cleavage of the IPGs caused by the enzyme GPI-PLD.

7. The method of claim 1 or 2, wherein the IPG antagonist is a competitive antagonist of the IPGs released from mast cells, basophils or eosinophils.

8. The method of claim 7, wherein when the composition is formulated for administration to a human patient, the competitive IPG antagonist is an IPG derived from a non-human species.

9. The method of claim 8, wherein the antagonist is an A-type IPG, which A-type IPG is obtainable from rat liver.

15. The method of claim 2, wherein the allergy comprises a seasonal allergy, a contact allergy, a drug allergy, a pollen allergy, or an insect allergy.

16. A method for inhibiting release of an IPG from a mast cell, a basophil or an eosinophil, the method comprising exposing the mast cell, the basophil or the eosinophil to an IPG antagonist.

17. The method of claim 16, comprising exposing the mast cell, the basophil or the eosinophil to an IPG antagonist in vitro.

18. The method of claim 16, comprising exposing the mast cell, the basophil or the eosinophil to an IPG antagonist in vivo.

19. The method of claim 18, comprising administering an effective amount of an IPG antagonist in a pharmaceutically acceptable excipient.

20. The method of claim 16, wherein the IPG antagonist comprises an anti-IPG antibody; a substance capable of inhibiting or preventing IPG release in mast cells, basophils or eosinophils; an inhibitor of the enzyme GPI-PLD; an antibody capable of inhibiting IPG release by inhibiting cleavage of the IPGs caused by the enzyme GPI-PLD; or a competitive antagonist of the IPGs released from mast cells, basophils or eosinophils.

APPENDIX C

"MARKED UP" PARAGRAPHS ILLUSTRATING THE AMENDMENTS MADE TO THE SPECIFICATION OF 09/601,971 WITH ENTRY OF THIS AMENDMENT

Paragraph on page 35 (new):

ABSTRACT OF THE DISCLOSURE

This application discloses that inositolphosphoglycans (IPGs) can be obtained from basophils, eosinophils and mast cells and that allergen stimulation of these cells results in IPG release. It also shows that IPGs are second messengers for allergic stimulation as the addition of some types of purified IPGs to non-allergen stimulated cells resulted in histamine release or degranulation. Thus, IPG antagonists can be used for treatment of conditions (especially allergy and asthma) mediated by the release of IPGs from mast cells, basophils or eosinophils. Preferred IPG antagonists include anti-IPG antibodies, inhibitors of the enzyme GPI-PLD and competitive antagonists.